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Real-life prospective study on asthma control in Italy: Cross-sectional phase results

Luigi Allegra [a], Giovanni Cremonesi [b], Giuseppe Girbino [c], Eleonora Ingrassia [b], Serafino Marsico [d], Gabriele Nicolini [b,*], Claudio Terzano [e], On behalf of the PRISMA (PRospectIve Study on asthMA control) Study Group

[a] *Thoracopulmonary Department, University of Milan, Fondazione IRCCS Cá Granda Ospedale Maggiore Policlinico, Via Francesco Sforza n. 28, 20122 Milan, Italy*
[b] *Medical Affairs Department, Chiesi Farmaceutici S.p.A., via Palermo 26/A, 43122 Parma, Italy*
[c] *Institute of Respiratory Medicine, University of Messina, Via Consolare Valeria, Gazzi, 98125 Messina, Italy*
[d] *Department of Respiratory Medicine, Azienda Ospedaliera Monaldi, Second University of Naples Via Leonardo Bianchi, 80131 Naples, Italy*
[e] *Respiratory Diseases Unit, Department of Cardiovascular and Respiratory Sciences, 'Sapienza' University of Rome, Viale del Policlinico 155, 00161 Rome, Italy*

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KEYWORDS
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Summary
Objectives: To estimate the prevalence of partly controlled and uncontrolled asthmatic patients, to evaluate quality of life and healthcare resource consumption.
Methods: Cross-sectional phase followed by a 12-month prospective phase. Asthma Control Test and the EQ-5D were used.
Results: 2853 adult patients recruited in 56 Hospital Respiratory Units in Italy were evaluated: 64.4% had controlled asthma, 15.8% partly controlled asthma and 19.8% were uncontrolled. The mean (SD) EQ-5D score was 0.86 (0.17) in controlled, 0.75 (0.20) in partly controlled and 0.69 (0.23) in uncontrolled patients ($p < 0.001$ between groups). The number of patients requiring hospitalization or emergency room visits was lower in controlled (1.8% and 1.6%, respectively) than in partly controlled (5.1% and 11.5%) and uncontrolled (6.4% and 18.6%). A combination of an inhaled corticosteroid and a long-acting beta-2 agonist was the reported therapy by 56.0% of patients, with the rate of controlled asthma and improved quality of life being higher in patients on extrafine beclomethasone/formoterol compared to budesonide/formoterol ($p < 0.05$) and fluticasone/salmeterol ($p < 0.05$ for quality of life).

* Corresponding author. Tel.: +39 0521 279561; fax: +39 0521 279592.
E-mail address: g.nicolini@chiesigroup.com (G. Nicolini).

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Conclusions: Asthma control is achieved in a good proportion of Italian patients. Differences may be detected in a real-life setting in favor of extrafine beclomethasone/formoterol combination.

Introduction

Asthma is a worldwide problem affecting more than 300 million people of all ages with a relevant impact on quality of life and healthcare resources.[1] International asthma guidelines[1,2] identify "asthma control" as the objective of treatment, i.e. achieving and maintaining control of symptoms and normal activity levels, maintaining pulmonary function as close to normal as possible, preventing asthma exacerbations and asthma mortality and avoiding adverse effects from asthma medications. The costs of asthma depend on the individual patient's level of control and the extent to which exacerbations are avoided.[1] GINA guidelines[1] define three different levels of asthma control (controlled, partly controlled or uncontrolled). Ongoing monitoring is essential in order to assess that control is reached and maintained for a prolonged period (at least 3 months) before modifying pharmacological treatment.[1]

In recent years, despite the availability of new pharmacological options and new combinations of existing drug therapies, the rate of suboptimal asthma control is still high. A population-based survey conducted in 11 European countries in the frame of the European Community Respiratory Health Survey II (ECRHS II),[3] demonstrated that 32% of patients had controlled asthma. Recently, a survey conducted in five European countries indicated that 50.4% of asthmatic patients were not well controlled[4] and this percentage increased to 56.6% in a more recent survey conducted in the same countries.[5] Although these data suggest lack of asthma control in about half of the patients, an unbiased comparison of data coming from different studies is difficult due to different asthma control measures and different data collection methods adopted. Actually, different questionnaires were used, not always standardized and validated and data were collected directly through patient self-administered or web based questionnaires whereas other studies included either office-based or hospital-based physician consultations.

Based on this background, and taking into consideration differences in data collection and in the instruments used to measure control, our multicenter, observational, cross-sectional and prospective study on asthma control (PRospectIve Study on asthMA control — PRISMA) was designed to estimate the level of disease control in Italy in adult asthmatic patients attending specialist centers. Secondary objectives were to understand the possible reasons for poor control, to assess quality of life and economic resources consumption in asthmatic patients with different levels of asthma control.

Methods

Study objectives

The PRISMA observational study protocol was designed to include a cross-sectional phase and a 12-month prospective phase in order to estimate the level of asthma control in real life and its evolution during a one year follow up. The main objective of the cross-sectional phase of the study was to estimate the prevalence of partly controlled and uncontrolled asthmatic patients in Italy and to describe the possible reasons for poor control. Further objectives of this phase were to assess the smoking rate of asthmatic patients, to collect information on anti-asthma treatments and their correlation with asthma control, to measure the amount of healthcare resources used in the 3 months preceding the first study visit, and to assess the relationship between level of asthma control as well as treatments taken at the time of the visit and quality of life. Patients with controlled asthma were not included in the longitudinal phase of the study.

Study population

Adult smoker and non-smoker asthmatic patients with a diagnosis of asthma for at least 6 months and attending 56 pneumology centers were enrolled between January and October 2009. Patients taking part in clinical trials or having completed a clinical trial in the 12 weeks preceding the study, those with serious or disabling concomitant diseases, and pregnant females were excluded.

Data collection and outcome measures

Data were collected by specialists interviewing consecutive outpatients. The Asthma Control Test (ACT) filled in by patients was used to assess the level of asthma control in the 4 weeks preceding the cross-sectional phase considering an overall score $\geq$20 controlled asthma, a score ranging from 16 to 19 partly controlled asthma, and a score $\leq$15 uncontrolled asthma.[2,6] Possible reasons for poor control were described according to doctors' opinion. When evaluation of asthma control was related to a specific drug class therapy, only patients who had been on that therapy for at least 5 consecutive days in the 3 months before the visit were included. For the comparison between treatments, only patients who had been on that therapy in the last 4 weeks were included in the analysis to match with ACT that evaluates asthma control in the last 4 weeks.

The following additional data were collected in the cross-sectional phase of the study (first visit): demographic data, education level (high level including senior secondary school and college/university graduates), smoking habits, occupational status, professional exposure to asthma risk factors/triggers (paint, dust, acids, inhalant gases and vapors), concomitant diseases, asthma history, health-related quality of life (HRQOL), past and ongoing asthma therapies, use of healthcare resources for asthma in the past 3 months (hospitalizations, emergency department admissions and medical consultations).

HRQOL was measured by the EQ-5D[7] filled in by patients and an appropriate algorithm[8] was used to summarize data in an overall score ranging from −1 (worse-than-death health status) to 1 (best health status).

Statistical methods

The sample size of the study was calculated to ensure a relative error of <30%: a confidence interval for the expected proportion was calculated using the large sample normal approximation. The literature shows that 48% of asthmatic patients have uncontrolled or partly controlled asthma, based on ACT[9] and that 5.1% of patients have optimal asthma control after one year of treatment.[10] Based on these figures, it was estimated that a sample of 2750 patients evaluable in the cross-sectional phase allowed one to observe the 95% confidence interval (CI) proportion of uncontrolled or partly controlled patients equal to 48% ± 1.87%. Furthermore, at least 1270 patients with uncontrolled or partly controlled asthma in the cross-sectional phase allowed one to observe the 95% CI proportion of patients reaching asthma control at the end of the one-year longitudinal phase of the study equal to 5.1% ± 1.40 (estimating a 25% drop-out rate and 953 evaluable patients).

Summary statistics (mean, standard deviation, median, minimum, maximum) were used for continuous variables, and absolute and relative frequency distribution was used for categorical data. The Chi square test (or Fisher exact test, when appropriate) was used to compare categorical variables among the controlled, partly controlled and uncontrolled cohorts of patients, while comparisons of continuous variables were performed by means of the Kruskal–Wallis test. Post-hoc comparisons were performed, when applicable: in such instances, Bonferroni's correction was applied. Logistic regression was used to compute odds ratio (OR), where the dichotomous outcome was the asthma control (controlled vs partly controlled + uncontrolled) and the independent variable was the pharmacological treatment. Multivariate analyses were also performed to assess the relationship between HRQOL/resource use and asthma control with the inclusion of additional covariates. Covariates were chosen a priori for all models on the basis of clinical relevance, which included age, gender (male, female), educational level (low level/high level), BMI, asthma risk factors/triggers in the occupational environment (yes, no), smoking habits (smokers, ex-smokers, non-smokers), concomitant diseases (yes, no). Multicollinearity among explanatory variables was investigated to ensure no correlations between variables. Multiple logistic regression was used in investigating the association between resource use (outpatients visits, hospitalization admission, emergency dept. visits) and asthma control, taking into account the aforementioned covariates. Similarly, multiple linear regression models were applied for HRQOL (EQ-5D score, EQ-5D VAS score); in this case variables were standardized. Significance was set at a two-tailed p value of 0.05.

Ethics

The study was carried out in conformity with Italian rules on the conduction of observational studies. Patients gave their written informed consent prior to study participation. The study was approved by the Institutional Review Board in all participating centers.

Results

Characteristics of patients and asthma control

Among 2853 patients enrolled in 56 pneumology centers across Italy 64.4% were controlled, 15.8% were partly controlled and 19.8% were uncontrolled (Table 1).

The main reasons for poor control were low adherence to treatment in 43.3% of patients, exposure to irritants/triggers in 29.0%, unsatisfactory patient–doctor communication in 21.2% and inadequate prescribed therapy in 19.9% of cases. The smoking rate was higher among uncontrolled (21.2%) than among partly controlled (17.1%) or controlled patients (14.1%) with an opposite trend in non-smokers and ex-smokers (77.4% uncontrolled, 84.7% partly controlled and 85.2% controlled; overall $p = 0.0001$).

Patients exposed to asthma risk factors/triggers in the occupational environment were 18.9%, with a higher rate being observed in uncontrolled (28.1%) compared to partly controlled (21.5%) and controlled (15.4%) patients (overall $p < 0.0001$).

High-level education was reported in 52.8% of patients and was associated with a higher level of asthma control when compared to low educational level (Table 1). Approximately half of the patients in employable age were employed. The distribution of the proportion of controlled and uncontrolled patients as regards employment was not different (overall $p = 0.4752$).

The following concomitant diseases were more common in uncontrolled compared to controlled patients, respectively: gastro-oesophageal reflux (29.2% versus 18.6%; overall $p = 0.0001$), sinusitis (21.5% versus 11.3%; overall $p < 0.0001$), respiratory infections (7.9% versus 2.5%; overall $p < 0.0001$) and psychological disturbances (4.5% versus 1.0%; overall $p = 0.0003$). Male patients were more likely to be controlled (68.3% of all males) than partly controlled (14.8%) or uncontrolled (16.9%), when compared to females (61.9%, 16.4% and 21.6%, respectively; overall $p = 0.0014$). The percentage of obese patients (defined as body mass index ≥30) was higher in uncontrolled than controlled or partly controlled (overall $p = 0.0069$) with an opposite trend in patients with normal weight. The duration of asthma was longer in uncontrolled than controlled or partly controlled patients (overall $p = 0.0435$).

No other significant difference was observed among controlled, partly controlled and uncontrolled patients in the parameters considered (Table 1).

Pharmacologic treatments and asthma control

A total of 83.2% of patients reported taking pharmacologic asthma therapy for at least 5 consecutive days in the 3 months before the visit (Fig. 1). Fixed combinations between an inhaled corticosteroid and a long-acting beta-2 agonist (ICS/LABA) were the most used anti-asthma treatments, taken by 56.0% of patients. ICS were used by 11.5% of patients and leukotriene receptor antagonists (LTRAs) by 24.3%. LABA was used by 22.2% of patients.

Table 1 Patients characteristics.

	No. of evaluable subjects: 2853	Controlled $n = 1836$	Partly controlled $n = 451$	Uncontrolled $n = 566$	Overall p value
Age, years, mean (SD)	46 (16)	46 (16)	45 (15)	47 (15)	0.3715
Age categories, *n* (%)					0.1614
≥65 years	404 (14.2)	271 (14.8)	53 (11.8)	80 (14.1)	
40–64 years	1378 (48.3)	858 (46.7)	231 (51.2)	289 (51.1)	
18–39 years	1071 (37.5)	707 (38.5)	167 (37.0)	197 (34.8)	
Gender, *n* (%)					0.0014
Males	1083 (38.0)	740 (40.3)	160 (35.5)	183 (32.3)	
Females	1770 (62.0)	1096 (59.7)	291 (64.5)	383 (67.7)	
Level of asthma control, *n* (%)	2853 (100)	1836 (64.4)	451 (15.8)	566 (19.8)	NA
Reasons for lack of asthma control,[a] *n* (%)					NA
Poor adherence to therapy	440 (43.3)	–	194 (43.0)	246 (43.5)	
Continued exposure to irritants/triggers	295 (29.0)	–	124 (27.5)	171 (30.2)	
Poor patient–doctor communication	216 (21.2)	–	73 (16.2)	143 (25.3)	
Inadequate therapy	202 (19.9)	–	86 (19.1)	116 (20.5)	
Smoking habits	154 (15.1)	–	58 (12.9)	96 (17.0)	
Co-morbidities	154 (15.1)	–	72 (16.0)	82 (14.5)	
Inadequate inhalation technique	63 (6.2)	–	26 (5.8)	37 (6.5)	
Duration of asthma, years, mean (SD)	16.9 (13.4)	16.6 (13.6)	16.4 (12.7)	18.2 (13.2)	0.0435
Body mass index categories, *n* (%)					0.0069
Obese (>30 kg/m^2)	507 (17.8)	306 (16.7)	75 (16.6)	126 (22.3)	
Overweight (≥25 and <30 kg/m^2)	974 (34.1)	617 (33.6)	162 (35.9)	195 (34.5)	
Normal weight (≥18.5 and <25 kg/m^2)	1194 (41.9)	804 (43.8)	188 (41.7)	202 (35.7)	
Underweight (<18.5 kg/m^2)	75 (2.6)	43 (2.3)	12 (2.7)	20 (3.5)	
Not available	103 (3.6)	66 (3.6)	14 (3.1)	23 (4.1)	
Smoking habits, *n* (%)					0.0001
Smokers	455 (16.0)	258 (14.1)	77 (17.1)	120 (21.2)	
Non-smokers	1921 (67.3)	1284 (69.6)	287 (63.6)	350 (61.8)	
Ex-smokers[b]	454 (15.9)	280 (15.3)	86 (19.1)	88 (15.6)	
Not available	23 (0.8)	14 (0.78)	1 (0.2)	8 (1.4)	
Allergies, *n* (%)	1933 (67.8%)	1248 (68.0%)	317 (70.3%)	368 (65.0%)	0.2675
Concomitant diseases,[c] *n* (%)					<0.0001
Total	1609 (56.4)	969 (52.8)	287 (63.6)	353 (62.4)	
Rhinitis	903 (56.1)	541 (55.8)	164 (57.1)	198 (56.1)	
Cardiovascular diseases	396 (24.6)	245 (25.3)	70 (24.4)	81 (23.0)	
Gastro-oesophageal reflux	351 (21.8)	180 (18.6)	68 (23.7)	103 (29.2)	
Sinusitis	223 (13.9)	109 (11.3)	38 (13.2)	76 (21.5)	
Nasal polyposis	118 (7.3)	66 (6.8)	25 (8.7)	27 (7.7)	
Type II diabetes	89 (5.5)	50 (5.2)	14 (4.9)	25 (7.1)	
Respiratory infections	67 (4.2)	24 (2.5)	15 (5.2)	28 (7.9)	
Psychological disturbances	35 (2.2)	10 (1.0)	9 (3.1)	16 (4.5)	
Type I diabetes	11 (0.7)	6 (0.6)	2 (0.7)	3 (0.9)	
Other diseases	264 (16.4)	156 (16.1)	42 (14.6)	66 (18.7)	
Educational level, *n* (%)					0.0008
Low level	1143 (40.1)	702 (38.2)	177 (39.2)	264 (46.6)	
High level[d]	1507 (52.8)	1007 (54.8)	240 (53.2)	260 (45.9)	
Not available	203 (7.1)	127 (6.9)	34 (7.5)	42 (7.4)	
Employment status, *n* (%)					0.4752
Unemployed[e]	1370 (48.0)	888 (48.4)	226 (50.1)	256 (45.2)	
Employed	1383 (48.5)	889 (48.4)	213 (47.2)	281 (49.7)	
Not available	100 (3.5)	59 (3.2)	12 (2.7)	29 (5.1)	

Table 1 (*continued*)

	No. of evaluable subjects: 2853	Controlled $n = 1836$	Partly controlled $n = 451$	Uncontrolled $n = 566$	Overall p value
Exposure to asthma risk factors/triggers in the occupational environment, *n* (%)	538 (18.9)	282 (15.4)	97 (21.5)	159 (28.1)	<0.0001

NA = not applicable.
[a] Patients could have more than one reason.
[b] Patients who stopped smoking at least one year prior to study start.
[c] Patients could have more than one concomitant disease.
[d] High-level education includes senior secondary school and college/university graduates.
[e] Unemployed patients include students, retirees, unable to work, out-of-work, housewives or other.

ICS/LABA fixed combination therapy for at least 4 weeks was taken by 48.4% ($n = 1380$) of patients, equally distributed among extrafine beclomethasone/formoterol (BDP/F) ($n = 454$ patients, 32.9% of ICS/LABA fixed combinations), budesonide/formoterol (BUD/F) ($n = 453$, 32.8%) and fluticasone/salmeterol (FP/S) ($n = 473$, 34.3%) (Table 2).

Among patients treated with an ICS/LABA fixed combination, 72.1% had controlled asthma, whereas 13.7% were partly controlled and 14.2% were uncontrolled. The proportion of controlled patients was higher in patients treated with extrafine BDP/F than in those receiving BUD/F (Bonferroni's corrected $p = 0.0320$; Fig. 2). The odds ratio for being controlled was higher in patients treated with extrafine BDP/F than in those receiving the other two combinations ($p = 0.012$; Table 3).

Therapy with ICS/LABA fixed combination alone was reported by 782 patients (56.7% of patients on ICS/LABA) of which 77.9% had controlled asthma, 12.3% partly controlled and 9.9% uncontrolled asthma. Concomitant anti-asthmatic treatments were recorded in 43.3% of patients treated with ICS/LABA combinations. The most frequent was LTRAs reported in 28.6% with no differences among the three ICS/LABA combinations. A concomitant use of as needed short acting beta-2 agonists was found in 3.3% of patients treated with ICS/LABA combinations.

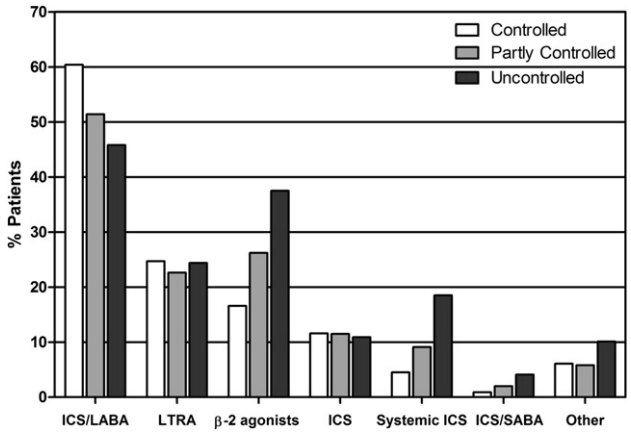

Figure 1 Treatment of asthma in the 3 months before the cross-sectional phase study visit. Data are percentage of patients in each category of asthma control reporting therapies for at least 5 consecutive days in the last 3 months; patients could have more than one pharmacologic class therapy; ICS: inhaled corticosteroids; LTRA: leukotriene receptor antagonists; CS: corticosteroids.

The mean [SD] daily dose of ICS in the three ICS/LABA fixed combinations was lower for extrafine BDP/F as compared to either BUD/F or FP/S (311.7 [109.5] μg, 590.1 [242.4] μg and 675.3 [342.9] μg, respectively; Bonferroni's corrected $p < 0.0001$; Fig. 3).

Health-related quality of life

The EQ-5D questionnaire and VAS were filled in by 2834 patients. The mean (SD) EQ-5D score was 0.86 (0.17) in controlled patients, 0.75 (0.20) in partly controlled and 0.69 (0.23) in uncontrolled patients. The mean (SD) of EQ-5D VAS score was 80.0 (12.7), 68.6 (14.9) and 61.5 (16.3), in the three subgroups, respectively. Both scores were higher (i.e. indicative of a better health status) in controlled than in uncontrolled or partly controlled patients (Bonferroni's corrected $p < 0.0001$), while partly controlled patients had higher mean scores than uncontrolled patients (Bonferroni's corrected $p < 0.0001$). These results were confirmed by multivariate regression: the adjusted regression coefficient of control was the highest for both EQ-5D scores (data are not shown). The mean EQ-5D score was higher in patients treated with extrafine BDP/F than in those receiving FP/S (Bonferroni's corrected $p = 0.018$; Fig. 4).

Healthcare resource consumption

Healthcare resource consumption due to asthma in the 3 months preceding the cross-sectional phase visit demonstrated that 46.5% of patients had an outpatient visit with either a general practitioner or a specialist, 6.5% had a visit in an emergency ward and 3.2% of patients were hospitalized (Fig. 5). The rate of patients who required admission to any type of healthcare service was lower in controlled patients than in uncontrolled and partly controlled (Bonferroni's corrected $p < 0.0001$). These results were confirmed by multivariate logistic regression: the adjusted OR for control was the highest for all healthcare services (data not shown).

Table 2 Characteristics of patients treated with ICS/LABA fixed combinations.

	No. of evaluable subjects: 1380	BDP/F extrafine $n = 454$	BUD/F $n = 453$	FP/S $n = 473$	Overall p value
Age categories, *n* (%)					0.0028
≥65 years	242 (17.5)	64 (14.1)	69 (15.2)	109 (23.0)	
40–64 years	707 (51.2)	237 (52.2)	237 (52.3)	233 (49.3)	
18–39 years	431 (31.2)	153 (33.7)	147 (32.6)	131 (27.7)	
Gender, *n* (%)					0.9379
Males	521 (37.8)	173 (38.1)	168 (37.1)	180 (38.1)	
Females	859 (62.3)	281 (61.9)	285 (62.9)	293 (62.0)	
FEV_1/FVC ratio, mean (SD)	0.76 (0.1)	0.76 (0.1)	0.76 (0.1)	0.75 (0.1)	0.2559
Level of asthma control, *n* (%)					0.0971
Uncontrolled	196 (14.2)	54 (11.9)	68 (15.0)	74 (15.6)	
Partly controlled	189 (13.7)	53 (11.7)	73 (16.1)	63 (13.3)	
Controlled	995 (72.1)	347 (76.4)	312 (68.9)	336 (71.0)	
Age at diagnosis of asthma, *n* (%)					0.3005
≤12 years	189 (13.7)	58 (12.8)	71 (15.7)	60 (12.7)	
>12 years	1093 (79.2)	368 (81.1)	348 (76.8)	377 (79.7)	
Not available	98 (7.1)	28 (6.2)	34 (7.5)	36 (7.6)	
Smoking habits, n (%)					0.1010
Smokers	200 (14.5)	78 (17.2)	69 (15.2)	53 (11.2)	
Non-smokers	922 (66.8)	289 (63.7)	305 (67.3)	328 (69.3)	
Ex-smokers[a]	256 (18)	87 (19.2)	78 (17.2)	91 (19.2)	
Not available	2 (0.1)	0 (0)	1 (0.2)	1 (0.2)	
Concomitant diseases,[b] *n* (%)					
Rhinitis	461 (56.2)	140 (57.1)	157 (57.1)	164 (54.5)	0.7650
Gastro-oesophageal reflux	180 (21.9)	48 (19.6)	71 (25.8)	61 (20.27)	0.1574
Sinusitis	116 (14.1)	26 (10.6)	48 (17.5)	42 (14.0)	0.0816
Nasal polyposis	74 (9.0)	24 (9.8)	24 (8.7)	26 (8.64)	0.8772
Respiratory infections	27 (3.3)	8 (3.3)	12 (4.7)	7 (2.3)	0.3911
Psychological disturbances	16 (2.0)	5 (2.0)	6 (2.2)	5 (1.7)	0.8961
Inhalant allergies, *n* (%)	873 (95.3)	274 (94.8)	309 (95.1)	290 (96.0)	0.7605
Concomitant therapies, *n* (%)	536 (38.8)	170 (37.4)	167 (36.9)	199 (42.1)	0.2024
Hospitalization, *n* (%)	43 (3.1)	14 (3.1)	16 (3.5)	13 (2.8)	0.7982
Outpatient visits, *n* (%)	620 (44.9)	192 (42.3)	203 (44.8)	225 (47.6)	0.2324
Access to Emergency Room, *n* (%)	60 (4.4)	21 (4.6)	22 (4.9)	17 (3.6)	0.6165
ACT score = 25, *n* (%)	203 (14.7)	73 (16.1)	62 (13.7)	68 (14.4)	0.5773

BDP/F = beclomethasone/formoterol; BUD/F = budesonide/formoterol; FP/S = fluticasone/salmeterol; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; ACT = asthma control test.

[a] Patients who stopped smoking at least one year prior to study start.

[b] Patients could have more than one concomitant disease.

Discussion

The main results of the cross-sectional phase of the PRISMA study are indicative of a high proportion of patients with asthma control in Italy attending specialist centers, distributed evenly over the country, representative of the national asthmatic population. An interesting finding of this study is related to the higher control level and better quality of life in patients treated with extrafine BDP/F as compared to BUD/F and FP/S.

Our results confirm previous evidence coming from a survey conducted in Italy between September 2005 and January 2006 showing a 64.7% of patients with an ACT score ≥20.[11]

A study published in 2008[12] comparing the level of asthma control evaluated by patients using a questionnaire with that reported by primary care physicians, highlighted that physicians estimated a higher level of control compared to patient-filled questionnaires. Notably, physicians overestimated control, regarding only 42% of patients as uncontrolled (instead of 59%), although they were more likely to report plans to alter the regimens of uncontrolled patients than controlled patients (1.29 versus 0.20 medication changes per patient) doing so in a fashion consistent with guideline recommendations. The high level of control we found in the present study is derived from ACT and EQ-5D questionnaires that were filled in by patients and, therefore, it is not likely to be overestimated.

The main reasons for poor control reported in our study were low adherence to treatment, exposure to irritants/triggers and unsatisfactory patient–doctor communication, while inadequate prescribed therapy accounted for poor

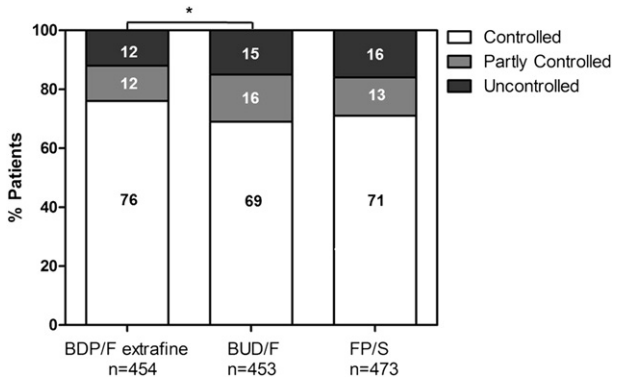

Figure 2 Percentage of patients treated with ICS/LABA fixed combinations with controlled, partly controlled or uncontrolled asthma; BDP/F = beclomethasone/formoterol; BUD/F = budesonide/formoterol; FP/S = fluticasone/salmeterol; *Bonferroni's corrected $p = 0.0320$ (for controlled vs partly controlled plus uncontrolled) vs BUD/F.

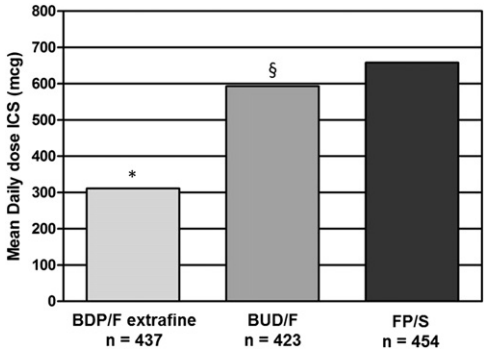

Figure 3 Mean daily ICS dose in patients treated with ICS/LABA combinations; BDP/F = beclomethasone/formoterol; BUD/F = budesonide/formoterol; FP/S = fluticasone/salmeterol; *Bonferroni's corrected $p < 0.0001$ vs BUD/F and FP/S; §Bonferroni's corrected $p < 0.0001$ vs FP/S.

asthma control in less than 20% of cases. Moreover, the population of our study included a significant proportion of smokers or ex-smokers and, in accordance with literature reports,[5] the data indicate that smoking is a critical factor associated with an increased risk of poor control[13,14] and an impaired corticosteroid response.[15] The evidence that smoking is correlated with an uncontrolled asthma status and that healthcare resource consumption, is higher in uncontrolled than in controlled patients are also in line with the data of previous surveys conducted in Italy.[11,16]

There is also confirmatory evidence that various comorbid conditions such as rhinosinusitis, gastro-oesophageal reflux disease, psychological disturbances and respiratory infections are often observed in asthmatic patients and may affect asthma control.[17] Based on this perspective, early identification of the clinical and behavioral factors responsible for poor asthma control[18] and interventions during routine outpatient visits for improving asthma trigger management, are strongly recommended.[19]

In agreement with previous findings,[5,16] asthma control was worse in women than in men. However, this gender effect was not confirmed in the international population-based survey ECRHS II conducted in 11 countries.[3] In contrast with other studies conducted in Europe and in Italy,[5,11] which showed that the probability of being uncontrolled increases with increased age, our data do not show a clear correlation between age ranges and level of asthma control. This finding is in line with the ECRHS II survey,[3] which reported a similar median age in categories of control. When compared to ECRHS II survey,[3] we found a greater proportion of controlled patients and this different finding can be due to several reasons. Data reported in the ECRHS II are derived from a sample of asthmatic patients selected from a general population survey which were invited to a local chest clinic to undergo a standardized clinical interview and allergologic and lung function tests. Asthma control was evaluated with the GINA guidelines composite measure, including lung function, whereas in our study asthma control was evaluated with the ACT that does not include lung function. This is probably the major difference leading to a lower proportion of controlled asthma in the ECRHS II study as compared to our data. Moreover, the sample population that was included in the ECRHS II study had a higher percentage of smokers (44% vs 16%), as compared to our study. Finally, the data of ECHRS II were collected 10 years ago and an improvement

Table 3 Odds ratio (OR) for controlled asthma in patients treated with ICS/LABA fixed combinations.

	OR	95% Wald CI	*p* value
BDP/F vs all combinations	1.391	1.075—1.801	0.012
BDP/F vs BUD/F	1.466	1.092—1.967	0.010
BDP/F vs FP/S	1.322	0.985—1774	0.062

BDP/F = beclomethasone/formoterol; BUD/F = budesonide/formoterol; FP/S = fluticasone/salmeterol; CI = confidence interval.

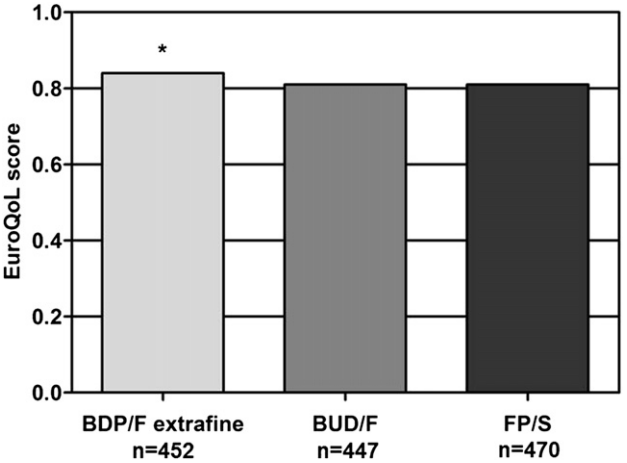

Figure 4 Results of EQ-5D score (ranging from 0 to 1) by ICS/LABA treatment (values are means); BDP/F = beclomethasone/formoterol; BUD/F = budesonide/formoterol; FP/S = fluticasone/salmeterol; *Bonferroni's corrected $p = 0.018$ vs FP/S.

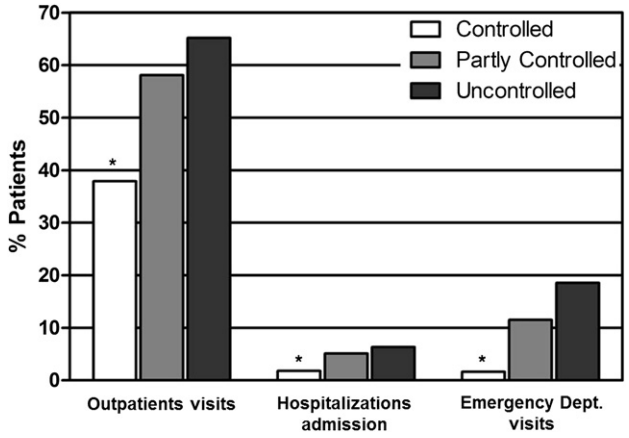

Figure 5 Admission to healthcare services due to asthma in the 3 months before the first visit (data are rates of patients); *Bonferroni's corrected $p < 0.001$ vs both partly controlled and uncontrolled patients (post-hoc analysis).

in asthma management and control could have occurred during time.

The analysis of our study data has provided robust evidence that uncontrolled and partly controlled patients have more frequent hospitalizations and emergency room visits and that their quality of life is poorer compared to controlled patients in agreement with previous findings.[9,10,16] Although age, gender, educational level, BMI, asthma risk factors/triggers in the occupational environment, smoking habits and concomitant diseases are all known to be related to both HRQOL and healthcare resource use, the effect attributable to control, even after adjustment, was still much higher.

The PRISMA data confirmed that asthma control can be achieved in a great proportion of patients treated with ICS/LABA fixed combinations, which were the most commonly used anti-asthmatic medications. This is in agreement with recent observational studies which show that ICS/LABA combinations are the most effective treatment choice.[20–22] When looking at the three available different combinations, differences both in asthma control and quality of life were detected in favor of the extrafine BDP/F fixed combination. Notably, patients under treatment with BDP/F extrafine combination were 40% more likely to be controlled as compared to BUD/F and FP/S, even if the clinical relevance of this difference is not clear. Actually, in a large randomized controlled trial (RCT) comparing BDP/F fixed combination with the same two drugs administered in large-particle formulations, a better asthma control was detected in the BDP/F fixed combination group and was considered to be related to the lung deposition profile of BDP/F extrafine formulation.[23]

The smaller particle size of the extrafine BDP/F combination, compared to BUD/F and FP/S combinations, both formulated with larger particles, enables ICS and LABA to effectively reach and treat both large and small airways, thus ensuring better treatment of inflammation and constriction in the entire bronchial tree and therefore leading to a greater clinical benefit. Indeed, the mass median aerodynamic diameter of BDP/F extrafine formulation is almost half the size of that in BUD/F and FP/S combinations.[24] Although RCTs are considered the most rigorous methods to investigate drug efficacy, their design limits the capacity to provide answers to questions about more "typical" patient populations and issues found only in clinical practice. By contrast, observational studies include larger and more diverse patient populations with common co-morbidities and can identify clinically important differences among treatments.[25] Asthmatic smokers, usually excluded from RCTs in asthma, were included in the PRISMA study. Asthmatic smokers are less responsive to ICS therapy and several mechanisms are postulated to explain impaired corticosteroid sensitivity in smokers with asthma.[15] Among these, impaired deposition of drug within the lungs that may reduce the local availability of ICS at key target cells within the airways has been suggested.[26] It has been demonstrated that tobacco smoke—drug particle interactions, contributing to the mechanisms of resistance, are less likely to affect the drug distribution within the lungs in the case of extrafine formulations,[27] suggesting that especially asthmatic smokers could benefit from extrafine drugs. In our study improved asthma control and quality of life was demonstrated for extrafine BDP/F combination despite the higher proportion of smokers in this group of patients. The greater benefits on asthma control and HRQOL with extrafine BDP/F fixed combination detected in the PRISMA study, that were not shown in previous comparative RCTs,[28,29] could be explained by the above considerations. Nevertheless, these findings should be interpreted with caution given the cross-sectional phase of the study and considering that treatments were started at variable times before the visit, however with a minimum time exposure of 1 month. However, no difference was found in the proportion of patients in terms of concomitant diseases, allergies or concomitant treatments for asthma among the three ICS/LABA combinations and the same was true for smoking status, age at diagnosis and FEV_1/FVC ratio.

Our results are also consistent with the results of a 12-month randomized trial that evaluated the HRQOL in patients with asthma who switched from large-particle BDP to extrafine BDP. According to this study, clinically important improvements in asthma-specific quality of life were observed for the extrafine treated group versus patients treated with large-particle BDP. According to the authors, improvements in the small airways with the extrafine formulation may be detected in the patient's quality of life but are not captured by conventional pulmonary function testing.[30]

This is confirmed by the results of a recent study conducted in an observational real-life context, concluding that initiating or increasing asthma controller therapy with an extrafine BDP formulation results in similar or better asthma control compared with non-extrafine FP, suggesting that the choice of formulation might result in clinically meaningful differences.[31]

Observational studies are limited by possible unmeasured or unrecognized confounding factors. We evaluated the possible role due to propensity to treat patients differently. Descriptive analyses did not shown any difference as regards gender, FEV_1, smoking habits and co-morbidities. We also think that recall bias was not a limit of our study as enrolled patients are affected by asthma and are sensitive to evoking their symptoms. However,

a strength of this study is that we included a large number of patients in a specific setting of Italian pneumology centers, evaluating asthma symptoms by means of a standardized questionnaire which has been recommended to be used by international guidelines.[1]

In conclusion, the cross-sectional phase of the observational PRISMA study indicated that asthma control can be achieved in a good proportion of patients and is associated with better quality of life and reduced health care resource consumption. ICS/LABA combination is the most common therapy and differences both in asthma control and in quality of life may be seen in a real-life setting showing better clinical outcomes in favor of extrafine BDP/F combination with the advantage of a more efficient ICS dose.

Conflict of Interest statement

Luigi Allegra: Consultant fees: GSK (I), Astrazeneca (I), Chiesi (I), Boehringer Mannheim (I), Zambon (I), IBSA (CH), Procter & Gamble (UK), Cotherix (USA). Reimbursements for attending a symposia: GSK (I), Astrazeneca (I), Chiesi (I), Boehringer Ingelheim (I), Eurodrug (NL) Angelini (I). Fees for speaking: Menarini (I), Boehringer Ingelheim (I), IBSA (CH), Eurodrug (NL). Funds for research: Angelini (I). Funds for members of staff: Cotherix (USA) Exalee (USA), IBSA (CH).

Giovanni Cremonesi: Employee of Chiesi Farmaceutici S.p.A.

Giuseppe Girbino: No conflict of interest.

Eleonora Ingrassia: Employee of Chiesi Farmaceutici S.p.A.

Serafino Marsico: No conflict of interest.

Gabriele Nicolini: Employee of Chiesi Farmaceutici S.p.A.

Claudio Terzano: No conflict of interest.

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Participants with significant contribution were: P. Bosco (Centro Catanese di Medicina e Chirurgia, Catania), M.Sforza (ASL BAT Andria, Andria), D. Ansalone (Ospedale G. da Procida, Salerno), D. De Sanctis (Ospedale di Atri, Atri), G. Failla (Ospedale Regina Apostolorum, Albano Laziale, Roma), V. Formisano (Ospedale Civile, Maddaloni, Caserta), A. Pennisi (Casa di Cura MUSUMECI Gecas, Gravina, Catania), W. Castellani (Ospedale Careggi, Firenze), M. Papale (I.F.O. Regina Elena, Roma), E. Giua Marassi (Ospedale Pneumologico R. Binaghi, Cagliari), R. Perra (I.N.R.C.A. Centro per le Broncopneumopatie IRCCS, Cagliari), E. Piccolini (Ospedale Santo Spirito, Casale Monferrato, Alessandria), S. Privitera (Centro per la Prevenzione e il Monitoraggio per l'insufficienza respiratoria, Giarre, Catania), R. Tazza (ASL4 Terni, Terni), M. Manzella (Servizio Territoriale di Pneumologia, San Severo, Foggia), G. Simon (Az. Osp. Villa Sofia CTO, Palermo), E. Marchi (I.N.R.C.A. Centro per le Broncopneumopatie, Casatenovo, Lecco), M. Nalin (Ospedale Santa Maria degli Angeli, Pordenone), V. Roncoroni (Ospedale Valduce, Como).

Participants were: F. Crismancich (Casa di Cura Pineta del Carso, Trieste), L. Ferramosca (Ospedale Civile Pispico, Poggiardo, Lecce), M. La Porta (Ospedale Ferro Branciforti Capra, Leonforte, Enna), N. Luzi (Ospedale Santo Spirito, Roma), B. Moscatelli (Ospedale San Giovanni Calibita FBF, Roma), S. Nardini (Ospedale Civile, Vittorio Veneto, Treviso), O. Resta (Policlinico Consorziale, Bari), P. Scavalli (Distretto 5 AUSL di Viterbo, Civita Castellana), A. Tubaldi (Ospedale di Macerata, Macerata), C. Zamprogna (Ospedale Amedeo di Savoia, Torino), A. Zedda (Ospedale S. Maria della Pietà Camilliani, Casoria, Napoli), V. Di Rienzo (ASL Frosinone, Frosinone), R. Numeroso (Casa di Cura Clinica San Carlo, Paderno Dugnano, Milano), E. Berardi (Ospedale M. Bufalini, Cesena), A. Scaramozzino (Policlinico Madonna della Consolazione, Reggio Calabria), G. Cremona (Istituto Scientifico San Raffaele, Milano), M. Torlasco (Ospedale Civile, Voghera), M. P. Foschino (Ospedale D'Avanzo, Foggia), O. Guarino (Ospedale S. Pietro Fatebenefratelli, Roma), G. Idotta (Ospedale Civile, Cittadella, Padova), R. Capra (Azienda Ospedaliera di Parma, Parma), L. Donateo (Azienda Unità Sanitaria Locale Lecce), M. Naldi (Ospedale San Donato, Arezzo), L. Bartolucci (Ospedale Narni-Amelia, Narni), V. Valenti (Policlinico San Donato, San Donato M.se), P. Rottoli (Az. Osp. Univ. Senese, Policlinico Le Scotte, Siena), P. Candoli (Ospedale Umberto I, Lugo, Ravenna), A. Moretti (Ospedale Sant' Andrea, La Spezia), M. Bevilacqua (Ospedale Civile CPO, Ostia, Roma), G. Cocco (A.O.R.N. A. Cardarelli, Napoli), R. Aquilina (Ospedale Unificato d'Imperia, Imperia).

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